2622-Pos Board B52
Using Kinetic Network Models to Understand Folding Mechanisms of GB1 Hairpin and its Trpzip Variants
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We used Markov State Model (MSM) approaches to analyze over 9 ms of explicit-solvent simulation trajectories for GB1 hairpin (the 16-residue C-terminal domain of protein G) and its three mutants (trpzip4, trpzip5, and trpzip6) at multiple temperatures, to investigate folding thermodynamics, kinetics, and mechanisms. Our MSM results show predicted folding rates and equilibrium populations that agree well with experimental data. Furthermore, we show how MSMs constructed from combined datasets reveal mechanistic differences resulting from tryptophan mutations. While wild type and trpzip4 hairpins are predicted to be two-state folders, our MSMs predict more complicated kinetics for trpzip5 and trpzip6 due to the presence of non-native traps. We find that changes in the folding landscape can also be revealed by analyzing MSM rate perturbations, provided that metastable states are conserved.

2623-Pos Board B53
Influence of Zinc-Binding on Folding and Dynamics of Zinc Finger Proteins: In Silico
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We present results of microsecond, all atom molecular dynamics simulations for various proteins including the zinc binding domains of NEMO and XIAP. Each zinc finger was simulated with and without zinc and with protonated and deprotonated zinc-binding cysteines. Simulation analyses suggest the bound zinc increases stabilization of the protein structure and causes changes to protein dynamics. In the absence of a bound zinc ion, proteins have a tendency to at least partially unfold and some simulations show complete loss of secondary structure. Differences in free energy of the four structural cases suggest that binding the zinc-ion is energetically inexpensive, where the (de)-protonation of the cysteines is the more significant contributor to free energy differences between the four structures.

2624-Pos Board B54
Folding Mechanism of Proteins IM7 and IM9, from Computer Simulations in a Realistic Atomistic Force Field
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IM7 and IM9 are small evolutionarily related proteins which fold according to different kinetics, in spite of their remarkable structural homology. While the former chain clearly folds according to three-state kinetics, the evidence for an on-pathway intermediate in the folding of IM9 is much more elusive. This observation has triggered considerable theoretical and experimental effort, aiming to characterize the folding pathways of these chains and clarify the physical origin of the observed differences. In this work, we use the Dominant Reaction Pathway (DRP) method to efficiently generate many folding trajectories for these proteins, from a realistic atomistic force field. Overall, our results are found to be in good agreement with with experimental φ-values and with the result of φ-value-restrained Molecular Dynamics (MD) simulation, and suggest that the differences in the folding pathways and kinetics is largely influenced by the chains' native topology. On the other hand,by performing MD simulations starting from the calculated on-pathway intermediates we argue that the difference in the life-times of the two on-pathway intermediates is due to non-native electrostatic interactions between specific residues and the solvent.

2625-Pos Board B55
Meltdown - a Tool for Classification and Analysis of DSF Data
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An application that translates raw thermal melt curve data into more easily assimilated knowledge is described. This program, called 'Meltdown', performs a number of data remediation steps before classifying melt curves and estimating melting temperatures. The final output is a report that summarizes the results of a differential scanning fluorimetry experiment. Meltdown uses a Bayesian classification scheme, enabling reproducible identification of various trends commonly found in DSF datasets. The goal of Meltdown is not to replace human analysis of the raw data, but to provide a sensible interpretation of the data to make this useful experimental technique accessible to naïve users, as well as providing a starting point for detailed analyses by more experienced users.

2626-Pos Board B56
Physics Based Structure Refinement in Casp11 using Geometric Unfolding and Hierarchically Restrained Replica Exchange Molecular Dynamics
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We have developed a new physics based approach to the protein refinement problem by mimicking the mechanism of chaperons that rehabilitate proteins. The template structure is unfolded by selectively pulling on different portions of the protein using the geometric based technique FRODA, and refolding the protein using hierarchically restrained replica exchange molecular dynamics. FRODA unfolding is used to create a diverse set of topologies for surveying near the native like structures from a template. The unfolding trajectories are then used to find energetic restraints to enforce contacts and dihedral restraints. An REMD simulation is performed for the entire ensemble using consensus and reservoir techniques, which allow multiple structural candidates to ''swap'' into the replica cascade at the highest temperature replica and the most favorable folds to propagate to the lowest temperature replica. The restraints are added in a hierarchical fashion where local contacts are restrained first followed by the addition of non-local restraints to narrow the conformational search toward the native state. After REMD structures are clustered, refined structures are selected based on the highest populated cluster, RMSD and DFIRE score.

2627-Pos Board B57
Role of Side Chain Size in the Formation of Secondary Structures in Model Peptides
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To study the role played by side chain interactions in -helix formation, we perform extensive all-atom molecular dynamics simulations of modified poly-alanine peptides in explicit TIP4P water. Our model systems include two poly-alanine peptide lengths (nine-mer and twelve-mer) described by the OPLS force-field in which we change systematically the value of the Lennard-Jones diameter, σ, and the well-depth, ε, of C_β atoms. We identify characteristic length-scales that promote -helices formation. To rationalize variations in -helix content observed in our simulations we computed effective interactions, i.e., potential of mean force (PMF) between methane-like particles that resemble side chains in our modified poly-alanine peptides. Contact-minimum, desolvation barrier, and solvent-separated-minimum of computed PMF(s) when superposed to distances between *i-i+1*, *i-i+3* and *i-i+4* neighbors are consistent in explaining qualitatively -helix content in our simulations. Implications of these results to the role of pressure in secondary structure formation are discussed.

2628-Pos Board B58
The Association Landscape of Ubiquitin Dimerization
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Ubiquitin is a highly conserved regulatory protein that acts as a post-translational modifier of various proteins in eukaryotes. For this, the C-terminus of ubiquitin is covalently linked to a lysine side chain of the target protein. Furthermore, ubiquitin can also form isopeptide-linked polymers, called polyubiquitin chains, which serve as versatile molecular signals regulating a vast range of cellular processes. Using molecular dynamics (MD) simulations and the Associated memory, Water mediated, Structure and Energy Model (AWSEM) coarse-grained model, we predicted the dimerization interface of two unconjugated ubiquitin monomers. Surprisingly, even without any covalent linkage ubiquitins recognized each other and formed a stable dimer. The obtained results are in strong agreement with experimental NMR data and provide detailed insights into the nature of ubiquitin's recognition and association.

2629-Pos Board B59
Roles of Urea and TMAO on the Interaction between Extended Non-Polar Peptides
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In this study, we investigate the role played by urea and trimethylamine n-oxide (TMAO) in the stability of extended poly-alanine and poly-leucine dimers using all-atom molecular dynamics simulations and the explicit TIP3P water